UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,455	12/29/2004	Didier M Raoult	935.44544X00	7537

20457 7590 12/21/2009

ANTONELLI, TERRY, STOUT & KRAUS, LLP
1300 NORTH SEVENTEENTH STREET
SUITE 1800
ARLINGTON, VA 22209-3873

EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
12/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,455	RAOULT, DIDIER M	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 23, 2009 has been entered.

Amendment Entry

2. The amendment filed September 23, 2009 has been entered. The examiner acknowledges the amendments to the specification. Claims 15, 20, 22, and 24 have been amended. Claims 1-14, 16 and 18 have been cancelled. Claims 15, 17 and 19-25 are under consideration in this office action.

Withdrawal of Rejections

3. The rejection of claims 20, 22 and 24 under 35 U.S.C. 112, second paragraph has been withdrawn in view of applicants' amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 15, 17, 19-21 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorval et al., (US Patent 5,561,045) in view of Hanke (DE 100 00 322A1, see the machine translation document from the EPO, pages 1-11).

Claim 15 is drawn to an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested, which comprises: a) depositing on a solid substrate a first antigen Ag_1 comprising a whole *Staphylococcus aureus* bacterium which comprises protein A and at least one second antigen Ag_2, wherein said second antigen Ag_2 is an infectious microbial agent, and b) contacting said first antigen Ag_1 and said at least one second antigen Ag_2 with a sample to be tested causing said first antigen Ag_1 and said at least one second Ag_2 to react with a sample to be tested, and c) detecting whether a human immunoglobulin Ac_1 in said human serum sample reacts with said first antigen Ag_1 by causing the reaction product Ag_1- Ac_1 to react with a detection substance, wherein said detection substance reacts with said human immunoglobulin and not with said first antigen (Ag_1), and wherein the reaction product Ag_1-Ac_1 is formed from the reaction of said human immunoglobulin Ac_1 and said first antigen Ag_1, and d) providing a controlled sample containing a human serum to be tested for detecting whether said detection

substance has reacted with the reaction product wherein said detection substance is a secondary detection antibody Ac_2 which is a labeled anti-human immunoglobulin which does not react with protein A and wherein said detection substance is labeled by fluorescent marking.

Claim 17 is drawn to the anti-human immunoglobulin being goat immunoglobulin or chick immunoglobulin. Claim 19 is drawn to the method further comprising: performing a series of tests at increasing dilutions of the sample to be tested with the detection substance Ac_1, wherein the detection substance Ac_2 is an immunoglobulin conjugated with a fluorescent substance, and verifying whether a reaction product Ag_1-Ac_1-Ac_2 can be detected by fluorescence at a dilution of the sample to be tested of 1/200 or less, wherein the reaction product Ag_1-Ac_1-Ac_2 is formed by the reaction of the human immunoglobulin Ac_1, the first antigen Ag_1, and the detection substance Ac_2. Claim 20 is drawn to the infectious microbial agent of Ag_2 is a microorganism selected from a bacterium, a virus, a parasite or a fungus. Claim 21 is drawn to the second antigen being an intracellular bacterium or a virus. Claim 24 is drawn to Ag_2 is H.I.V.

Claim 25 is drawn to a diagnosis kit for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested, which comprises: a solid substrate comprising a second antigen Ag_2 which is an infectious microbial agent, one positive controlling inclusion comprising a human serum in the sample to be tested which comprises a first antigen Ag_1 containing a whole *Staphylococcus aureus* bacterium containing protein A, and at least one reagent which can detect the presence of a reaction product of said first antigen with a human immunoglobulin Ac_1 comprising

a detection substance Ac_2 which comprises a labeled immunoglobulin which is an anti-human immunoglobulin which does not react with protein A.

Dorval et al., teach processes that permit the ability to detect simultaneously a variety of classes of immunoglobulin specific for the same analyte (col.2, lines 30-34). Dorval et al., teach the enhancement of sensitivity using specific binding proteins like Protein A within immunoassays (col. 2, lines 35-40). Dorval et al., teach anti-IgA-IgG and anti-IgM-IgG and protein A (col. 3, lines 19-20). Dorval et al., teach a solid support with a first antigen containing Protein A, a second microbial antigen, the addition of the detection agent which is labeled anti-human immunoglobulin with does not react with Protein A, see Figures 1a-1f. Dorval et al., teach a variety of kits with include the detection reagents, the binding protein A, and immunoglobulins (col. 4, lines 40-49). Dorval et al., teach labels to be chromophores, fluorophores, metal sols, enzyme labels and colorimetric particles (col. 6, lines 48-68). It is noted, that fluorescein is a common type of fluorophore. Dorval et al., teach the sensitivity of a wide variety of assays is enhanced with the use of the immunoglobulin and Protein A, including direct, indirect, competitive and sandwich type heterogeneous and homogenous assays (col. 9, lines 16-25). Dorval et al., teach the reagents may be advantageously in virtually any type of immunoassay where it is desirable to prevent the interaction of Protein A with a portion of an immunoglobulin; thus allowing the antigen to be bound to a solid phase and the presence of different classes of specific antibodies to be determined (col. 9, lines 25-33). Dorval et al., teach the detection of HIV virus (col. 9, lines 37-42).

Hanke teaches strips for western blotting which include on a carrier, (i) a serum control zone which will produce a band flowing incubation with patient serum and (ii) at least one conjugate control zone which will produce a band following incubation with a labeled anti-patient immunoglobulin antibody from a different animal species (abstract). Hanke teaches multiple control zones which make for improved differentiated, additional control possible and provides improved interpretation of test results (page 1 of the translation). Hanke teaches a labeled conjugated animal antibody which is specific for human immunoglobulin (page 2).

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the *in vitro* serological diagnosis method in which, in a sample to be tested, the presence is detected of antibodies specific to an infectious microbial agent, as taught by Dorval et al., wherein the modification incorporates the use a control zone as taught by Hanke in order to provide a method that establishes detection of human immunoglobulin interaction. Furthermore, there is a reasonable expectation of success in incorporating the methods of Dorval et al., and Hanke since both teach providing a sample to be tested is react with solid-substrate having a deposited first and second antigen and detecting whether the human immunoglobulin reacts with the antigen, especially when no change in their respective functions, thus the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Dorval et al., and Hanke while incorporating the additional bacterial and viral pathogens into the *in vitro*

serological diagnosis as in order to arrive at the claimed invention with provide assays containing serum and conjugate control zones when detecting infectious microbial antigens.

Response to Arguments

5. Applicant's arguments filed September 23, 2009 have been fully considered but they are not persuasive.

Applicants respectfully submit that the Dorval et al. document is directed to a method for simultaneously detecting immunoglobulins including IgG, IgA and/or IgM and not to an in vitro serological diagnosis for detecting antibodies specific to an infectious microbial agent. In response to applicant's argument that Dorval et al., is detected to detecting antibodies, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). This argument is not persuasive since both the instant claims and Dorval et al., detect the present of specific antibodies. Furthermore, Dorval et al., teach each and every recited limitation.

Applicants respectfully submit that to the allegation that the "addition of a detection agent which is a labeled antihuman immunoglobulin which does not react with protein A" is not taught nor suggested by the Dorval et al. Dorval et al., the advantageous detection of immunoglobulins or antibodies using labeled anti-IgA-IgG to determine the presence of IgA, similarly, anti-IgM-IgG is used to determine IgM.

Furthermore, Dorval et al., teach using labeled Protein A would bind the labeled anti-IgA-IgG causing aggregation and hinder the assay (col. 5, lines 50-62). Additionally, Dorval teaches indirect detection, which meets the instant limitations. Finally, Dorval et al., teach the detection reagent formulation where the detection reagent, and the presence of IgM, IgA and/or IgG are determined without unwanted binding between any species in the detection reagent and any analyte or between any two species in the detect reagent (col. 4, lines 55-61). Therefore the addition of a detection agent which is a labeled antihuman immunoglobulin which does not react with protein A is taught by Dorval et al.

Applicants point to Figures 1A-1F where the detection reagent includes protein A (36) coupled to a hydrophobic label, specifically indigo. However the figure 36 is not a secondary detection antibody as now recited by the instant claims, therefore applicants' argument is not persuasive.

It is the position on of the Office that Dorval et al., teach the detection reagent formulation where the detection reagent, and the presence of IgM, IgA and/or IgG are determined without unwanted binding between any species in the detection reagent and any analyte or between any two species in the detect reagent (col. 4, lines 55-61). Dorval et al., state that the detection reagent may be prepared where each of the labeled anti-IgA and anti-IgM are coupled to a blocking agent blocking interaction of the labeled immunoglobulin with Protein A. Additionally, virtually any type of immunoassay where it is desirable to prevent the interaction of Protein A with the Fc portion of an immunoglobulin is advantageous (col. 9,lines 25-30). Furthermore, Hanke teaches

using specific binding and a secondary antibody for indirect detection where the labeled antibody is against the primary antibody. And it is noted that the secondary antibody is not specific for Protein A, but for the primary antibody. Hank teaches that indirect immune detection has a higher sensitivity. Thus the argument is not persuasive.

Applicants also respectfully submit that there is nothing in the Dorval et al. document that teaches or suggests that the protein A can be used as a control antigen for determining whether or not a negative serum sample is due to the absence of reaction with a serum, let alone a controlled sample to be tested containing a human serum. It noted that the instant specification at page 4 states that it is well known in the art that *S. aureus* has already been added to serological test as a detector antigen for antibodies. Contrary to Applicants assertion, Dorval et al., state that IgG of all specificities has been captured at first immobilized assay reagent area by immobilized Protein A, serving as a control, as IgG is present in large amounts in all serum samples (col. 11, lines 6-11). Therefore, even though the claims do not actually recite using Protein A as a control, Dorval et al., still teach using Protein A as a control during microbial serology reactions.

Applicants respectfully submit that Hanke neither teaches nor suggests the claimed invention. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one

of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been *prima facie* obvious at the time of applicants invention to modify the *in vitro* serological diagnosis method in which, in a sample to be tested, the presence is detected of antibodies specific to an infectious microbial agent, as taught by Dorval et al., wherein the modification incorporates the use a control zone as taught by Hanke in order to provide detection of additional microbes into the *in vitro* serological diagnosis while assaying serum samples on conjugate control zones when detecting infectious microbial antigens.

Finally, Applicants argue that neither Dorval et al., or Hanke teach or suggest a method or kit for detecting whether the tested sample contains a human serum. Contrary to applicants' assertion Dorval et al., in Example 7, teach the procedure for assembling a test assay kit and with the same components taught throughout the specification. See also column 4, lines 40-46 which is drawn to the a wide variety of kits including detection reagents, proteins that to a binding site on the immunoglobulin, immunoglobulins that specifically bind to a predetermined analyte and a binding site for the protein on that immunoglobulin being blocked. Therefore Applicants arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorval et al., (US Patent 5,561,045) and Hanke (DE 100 00322) in view of La Scola et al (Journal of Clinical Microbiology, 1996; 34(9): 2270-2274).

Claim 22 is drawn to the second antigen being Chosen from among bacteria of the genus *Rickettsia, Coxiella, Bartonella, Tropheryma, Ehrlichia, Chlamydia, Mycoplasma, Treponema, Borrelia,* and *Leptospira.* Claim 23 is drawn to the second antigen corresponding to the infectious microbial agent is a bacterium responsible for endocarditis.

Dorval et al., and Hanke have been discussed above, however neither teach the second antigen being *Bartonella* or a bacterium being responsible for endocarditis.

La Scola et al, teach serological cross-Reactions *between Bartonella Quintana, Bartonella henselae,* and *Coxiella burnetti. Bartonella Quintana,* is known to be associated with endocarditis, while *Bartonella henselae* is known to be associated diseases in AIDS patients (page 2270).La Scola et al., teach a method of performing serological diagnostic test for *Bartonella* and *C. burnetti* infections (page 2270). The prior art discloses immunoglobulin G (IgG) anti-phase I titer of equal to or greater than 1:800 and an IgA anti-phase II titer were considered diagnostic for infection. La Scola et al teach that human patients with titers of equal to or greater that 1:1,600 or antibody against *B. henselae* or *B. Quintana* antigens were also considered diagnostic for

infection (page 2272). La Scola et al., teach positives being found (IgG, 1:100) (IgG 1:200) (page 2271). The method of La Scola et al comprises the following steps: a) Serum samples were taken from patients; b) Bacterial antigen being deposited on 30 well microscope slides, and sera was serially diluted and applied to the wells; c) Slides were incubated in a moist chamber for 30 minutes, washed, dried and overlaid with labeled goat anti-human IgG antibodies; d) Interaction of antigen and antibody was observed (page 2271). La Scola et al., teach Western blotting was used to determine the interaction of antigen and antibody (page 2271).

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the *in vitro* serological diagnosis method in which, in a sample to be tested, the presence is detected of antibodies specific to an infectious microbial agent, as taught by Dorval et al., and Hanke wherein the modification incorporates the use of variety of microbial agents as taught by La Scola et al., in order to provide detection of a wide variety of agents. Furthermore, there is a reasonable expectation of success in incorporating the methods of Dorval et al., and Hanke in view of La Scola et al., since both teach providing a sample to be tested is react with solid-substrate having a deposited first and second antigen and detecting whether the human immunoglobulin reacts with the first antigen, especially when the steps and components of the method have been combined with no change in their respective functions, thus the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Dorval et al., and Hanke

while incorporating the additional yet equivalent microbial antigens associated with AIDS and HIV into the *in vitro* serological diagnosis as taught by Dorval and Hanke in order to arrive at the claimed invention with provide enhanced sensitivity using specific binding proteins like Protein A within immunoassays.

Response to Arguments

7. Applicant's arguments filed September 23, 2009 have been fully considered but they are not persuasive.

Applicants respectfully submit that La Scola et al. neither teach nor suggest a method or kit for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested using a whole *Staphylococcus aureus* as recited in the claims of the present invention. However it is noted that Dorval et al., and Hanke have been discussed above as meeting the limitations of claims 15 and 20. And Applicants is reminded that claim 22 is drawn to the second antigen being chosen from among bacteria of the genus *Rickettsia, Coxiella, Bartonella, Tropheryma, Ehrlichia, Chlamydia, Mycoplasma, Treponema, Borrelia,* and *Leptospira;* while Claim 23 is drawn to the second antigen corresponding to the infectious microbial agent is a bacterium responsible for endocarditis. Thus applicants' arguments are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is a reasonable expectation of success in incorporating the methods of Dorval et al., and Hanke in view of La Scola et al., since both teach providing a sample to be tested is react with solid-substrate having a deposited first and second antigen and detecting whether the human immunoglobulin reacts with the first antigen, especially when the steps and components of the method have been combined with no change in their respective functions, thus the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Therefore the arguments are not persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 15, 17 and 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 15,(c) recites the limitation "the reaction product" in the claim. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645